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TRANSDERMAL APPLICATION AGENT CONTAINING 3-KETO-DESOGESTREL

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(57) Claim

1. Agent for transdermal administration, characterized in that it contains 3-keto-desogestrel, optionally in combination with one or more estrogen(s), together with a transdermal therapeutic system comprising two or three matrix layers adhering to a cover coating.

2. Agent for transdermal administration according to claim 1, wherein as estrogen(s), estradiol, estriol, 17α-ethinylestradiol, mestranol, 14α, 17α-ethanoestra-1,3,5(10)-triene-3β, 17α-diol, 14α, 17α-ethanoestra-1,3,5(10)-triene-3β, 16α, 17α-triol or esters of these compounds are used.

3. Agent for transdermal administration according to claim 2, wherein the transdermal therapeutic system consists of

   a) an impermeable cover coating,

   two or three matrix layer(s) adhering to the cover coating, containing the 3-keto-desogestrel, optionally estrogen(s) and optionally penetration-enhancing agents, permeable and self-adhesive for these components or covered or surrounded by a skin contact adhesive optionally containing penetration-enhancing agents, a removable protective layer, or

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b) a covering provided with a contact adhesive optionally containing penetration-enhancing agents,

two or three matrix layer(s) (each) leaving uncovered a contact adhesive edge, attached by an impermeable covering to the contact adhesive, containing the 3-keto-desogestrel, optionally estrogen(s) and penetration-enhancing agents, and a removable protective layer, or

c) an impermeable cover coating,

two or three pharmaceutical agent reservoir(s) present on or in the cover coating and containing the 3-keto-desogestrel, optionally estrogen(s) and optionally penetration-enhancing agents,

two or three skin contact adhesive layers containing polymer layer(s), permeable to these components, of an optionally permeable penetration-enhancing agent, and a removable protective layer.

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(54) Title: TRANSDERMAL APPLICATION AGENT CONTAINING 3-KETO-DESOGESTREL

(54) Bezeichnung: MITTEL ZUR TRANSDERMALEN APPLIKATION ENTHALTEND 3-KETO-DESOGESTREL

(57) Abstract

A transdermal application agent is characterized in that it contains 3-keto-desogestrel, if required combined with one or two estrogens.

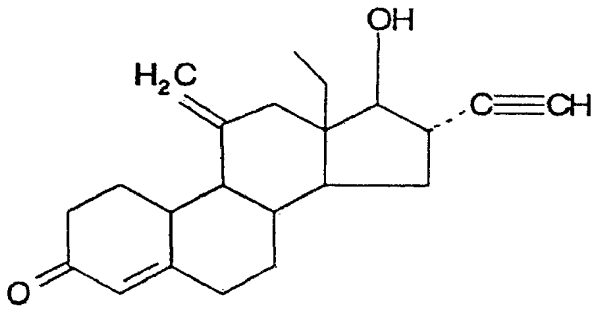
(57) Zusammenfassung

Ein Mittel zur transdermalen Applikation wird beschrieben, welches dadurch gekennzeichnet ist, daß es 3-Keto-desogestrel gegebenenfalls in Kombination mit einem oder zwei Östrogen(en) enthält.

Agent for Transdermal Administration Containing 3-Keto-desogestrel

The invention relates to an agent for transdermal administration, characterized in that it contains 3-keto-desogestrel optionally in combination with one or more estrogen(s).

3-Keto-desogestrel (13-ethyl-11-methylene-17ß-hydroxy-18,19-dinor-17α-pregnen-3-one) is a substance of formula



As is generally known, it is a pharmacologically effective compound with extraordinarily strong gestagenic effectiveness, which is used in the form of its prodrug desogestrel (J. of Steroid Biochem., 14, 1981, 175 ff and Europ. J. Clin. Pharmakol. 15, 1979, 349 ff) in combination with estrogenically effective compounds for the production of agents of contraceptive action to be administered orally (Marvelon(R)).

It has now been found that 3-keto-desogestrel optionally in combination with one or more estrogen(s) can be used very well for the production of an agent for the transdermal administration

of the active ingredient or active ingredient mixture. In principle, the desogestrel itself could also be administered transdermally. But 3-keto-desogestrel is to be preferred because of its higher potency of action.

As is generally known, pharmaceutical agents to be administered transdermally have the advantage that they make possible a more uniform release of the active ingredient over a prolonged period than is generally possible in other agents to be administered -- such as, for example, perorally. These properties can generally be used advantageously in a number of endocrine diseases. But for slightly water-soluble steroid hormones, such as, for example, the gestagens, it is generally quite problematical to provide transdermal systems that assure a penetration of the active ingredient through the skin sufficient for treatment.

It has now been found that it is surprisingly possible with the help of the agent according to the invention to achieve a therapeutically adequate, very uniform rate of penetration of the steroid hormones through the skin, while this is only conditionally possible in the known steroid hormones containing agents to be administered transdermally (EP-A 137278 and EP-A 275716), which makes necessary the use of comparatively large systems.

Suitable estrogens for the agent according to the invention are, for example, the estradiol, the estriol, the ethinylestradiol, the mestranol, the 14α,17α-ethanoestra-1,3,5(10)-triene-3β,17α-diol (WO 88/01275), the 14α,17α-

ethanoestra-1,3,5(10)-triene-3ß,16α,17α-ethanoestra-1,3,5(10)-triene-3ß,16α,17α-triol (WO91/08219) and their esters (EP-A 163596), such as the estradiol-dipropionate, the estradiol-dihexanoate and the estradiol-didecanoate. In addition to the 3-keto-desogestrel, the combination preparations according to the invention preferably contain 1 to 3 -- especially 1 to 2 -- estrogen(s).

For the production of pharmaceutical preparations, the active ingredient or the active ingredient mixture can be dissolved or suspended in suitable volatile solvents and/or penetration-enhancing agents. The solutions or suspensions obtained can be mixed with the usual adjuvants, such as matrix formers and bactericides, and optionally can be bottled after sterilization in usual metering tanks. But on the other hand, it is also possible to further process these solutions or suspensions to lotions or ointments with inclusion of emulsifiers and water. Sprays can also be produced -- optionally by adding propellant -- which can be bottled in the usual metering tanks.

Suitable volatile solvents are, for example, lower alcohols, ketones or lower carboxylic acid esters, such as ethanol, isopropanol, acetone or ethyl acetate, polar ethers, such as tetrahydrofuran, lower hydrocarbons, such as cyclohexane or benzine, or else halogenated hydrocarbons, such as dichloromethane, trichloromethane, trichlorotrifluoroethane and trichlorofluoromethane. There is no need for an explanation that mixtures of these solvents are also suitable.

Suitable penetration-enhancing agents are, for example, monovalent or multivalent alcohols, such as ethanol, 1,2-propanediol or benzyl alcohol, saturated and unsaturated fatty alcohols with 8 to 18 carbon atoms, such as lauryl alcohol or cetyl alcohol, hydrocarbons, such as mineral oil, saturated and unsaturated fatty acids with 8 to 18 carbon atoms, such as stearic acid or oleic acid, fatty acid ester with up to 24 carbon atoms or dicarboxylic acid diesters with up to 24 carbon atoms.

Fatty acid esters, which are suitable for the agent according to the invention, are, for example, those of acetic acid, caproic acid, lauric acid, myristic acid, stearic acid and palmitic acid, such as, for example, the methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-butyl ester, isobutyl ester, tert-butyl ester or monoglyceric acid esters of these acids. Especially preferred esters are those of myristic acid or oleic acid, such as their methyl esters and especially their isopropyl esters. Suitable dicarboxylic acid diesters are, for example, the diisopropyl adipate, diisobutyl adipate and diisopropyl sebacate.

Other penetration-enhancing agents are phosphatide derivatives, such as the lecithin, terpenes, amides, ketones, urea and its derivatives or ethers, such as, for example, dimethyl isosorbide and diethylene glycol monoethyl ether. There is no need for a more detailed explanation that also mixtures of these penetration-enhancing agents are suitable for the production of the agent according to the invention.

The concentration, in which the active ingredient or the active ingredient mixture optimally is dissolved or suspended in the solvent, is usually 0.01 to 25% by weight for 3-keto-desogestrel. In estrogens, the concentration depends, by the nature of things, on the type of active ingredient used and the single dose sought, it must be determined in individual cases by the preliminary tests familiar to one skilled in the art, such as, for example, the determination of the achievable plasma concentrations of active ingredient after dermal application, in the case of selected agents according to the invention. In general, active ingredient concentrations of 0.01 to 25% by weight of estrogen in agents according to the invention will be sufficient here, too. The weight ratio of 3-keto-desogestrel to estrogen or estrogens is approximately 5:1 to 1:10 in the combination preparations.

For oral contraception, the gestagenic daily dose is 150 µg of desogestrel, which is converted almost completely to the pharmacologically active 3-keto-desogestrel during the absorption. The contraceptive daily dose could be lowered to about 60 µg of 3-keto-desogestrel by incorporation of 3-keto-desogestrel in a subcutaneous depot (Implanon (R)) (Contraception 47, 1993, 251-261), because of a relatively constant rate of release. To make this daily dose of 60 µg of 3-keto-desogestrel bioavailable by transdermal routes with a TTS of 10 cm^2 area, a transdermal flow of about 250 $\mu g/cm^2/h$ is required.

The determination of the extent of the speed of the percutaneous resorption of [3H]-3-keto-desogestrel through the

full-thickness skin of a hairless mouse can be made by the Franz flow chamber.

With the help of the Franz chamber battery, the time behavior of the [3H]-radioactivity in the compound liquid, hemisotonic polyethylene glycol 400, which contains 1000 I.U. of penicillin per ml, is determined.

Three experiments are performed per batch, in which in each case two formulations are examined in three Franz chambers, which are strung with full-thickness skin of a hairless mouse. Per skin area (0.32 cm^2), 200 μg of 3-keto-desogestrel, which is dissolved or suspended in 10 μl of formulation, is administered with an Eppendorf pipette.

The sampling of the receptor liquid takes place every two hours, for a total of 48 hours.

The table below shows the results obtained in these tests.

Percutaneous Flow of 3-Keto-desogestrel-containing Formulations in ng/cm²/h

Test	Formulation in	average flow on 1st day	average flow on 2nd day	max. flow
A	1,2-propanediol	920 ± 539	1316 ± 572	1975 ± 765
B	95% 1,2-propanediol + 5% laurocapsam*	3606 ± 695	3748 ± 468	4440 ± 808
C	90% 1,2-propanediol + 10% lauric acid	3855 ± 994	4892 ± 928	5033 ± 942
D	90% 1,2-propanediol + 10% lauryl alcohol	4885 ± 1261	5245 ± 928	5899 ± 1361
E	isopropyl myristate	2184 ± 354	2743 ± 193	3002 ± 247
F	propylene glycol-monolauric acid ester	1531 ± 562	2464 ± 530	2626 ± 599

*Azone (R) of the Nelson Corp.

It is seen that the therapeutically necessary daily dose is easily achieved or even exceeded.

A very uniform administration with set metering of the active ingredient or active ingredient mixture can be achieved if the active ingredient or the mixture is embedded in a transdermal

therapeutic system (TTS). Suitable transdermal therapeutic systems are those that are usually used for percutaneous administration of active ingredients (Yie W. Chien: "Transdermal Controlled Systemic Medications," Marcel Dekker, Inc., New York and Basel, 1987, Dr. Richard Baker: "Analysis of Transdermal Drug Delivery Patents 1934 to 1984" and "Analysis of Recent Transdermal Delivery Patents, 1984-1986 and Enhancers" Membrane Technology & Research 1030 Hamilton Court Menlo Park CA 94025 (415) 328-2228).

Thus, for example, a transdermal therapeutic system can be used, which consists of

a) an impermeable cover coating,

two or
~~one to~~ three matrix layer(s) adhering to the cover coating, containing the 3-keto-desogestrel, optionally estrogen(s) and optionally penetration-enhancing agents, permeable and self-adhesive for these components or covered or surrounded by a skin contact adhesive optionally containing penetration-enhancing agents, a removable protective layer, or

b) a covering provided with a contact adhesive optionally containing penetration-enhancing agents,

two or
~~one to~~ three matrix layer(s) (each) leaving uncovered a contact adhesive edge, attached by a covering to the contact adhesive, containing the 3-keto-desogestrel, optionally estrogen(s) and penetration-enhancing agents, and a removable protective layer, or

c) an impermeable cover coating,

two or
~~one to~~ three pharmaceutical agent reservoir(s) present on or in the cover coating and containing the 3-keto-desogestrel, optionally estrogen(s) and optionally penetration-enhancing agents,

two or
~~one to~~ three skin contact adhesive layers containing polymer layer(s), permeable to these components, of an optionally permeable penetration-enhancing agent, and a removable protective layer.

A transdermal therapeutic system according to variant a) represents a simple matrix system. It can be, for example, of round, oval or rectangular shape and produced as follows.

A solution or suspension of up to 25% by weight of active ingredient or active ingredient mixture, 0-40% by weight of a penetration-enhancing agent, 30-70% by weight of a medicinally usual adhesive filled up with a suitable volatile solvent to 100% by weight is coated with a plane, impermeable cover coating. After the drying, a second and optionally later even a third layer, optionally containing active ingredients, penetration-enhancing agents and adhesives, can be applied on this layer and dried. Then, the matrix system is provided with a removable protective layer.

If a medicinally usual matrix former is used, which does not adhere or insufficiently adheres to the skin after the drying of the system, the system can be covered or surrounded in addition with a skin contact adhesive before the application of the removable protective layer.

Suitable solvents and penetration-enhancing agents are, for example, the already mentioned liquids of this type. As medicinally usual adhesives, for example, polyacrylates, silicones, polyurethanes, block polymers, styrene-butadiene copolymers as well as natural or synthetic rubbers, such as, e.g., polyisobutylenes, are suitable. As additional matrix formers, cellulose ether, polyvinyl compounds or silicates are to be considered. To increase the stickiness, the usual additives, such as, for example, tackifying resins and oils, can be added to the matrix obtained.

As protective layers, all films are suitable that are usually used in transdermal therapeutic systems. Such films are, for example, siliconized or fluoropolymer-coated.

As cover coating, for example, 10 to 100 μm-thick films made of polyethylene or polyester can be used selectively pigmented or metallized in this system. The pharmaceutical agent layer applied on it preferably has a thickness of 20 to 500 μm. The release of the active ingredients takes place preferably over an area of 5 to 100 cm^2.

In the case of multilayer matrix systems, the 3-keto-desogestrel and optionally the penetration-enhancing agents can be introduced in the matrix applied on the impermeable cover coating, while the layer or layers below contains the estrogens and optionally also penetration-enhancing agents. But on the other hand, it is also possible in such a transdermal system to arrange several active ingredient-containing matrix systems side by side.

A transdermal therapeutic matrix system according to variant b can be, for example, also round, oval or rectangular and can be produced as follows.

A covering is coated with a skin contact adhesive. Then, one to three punched-out areas of a matrix layer provided with an impermeable covering, the 3-keto-desogestrel, optionally containing estrogen(s) and penetration-enhancing agents, is bonded to the covering pro TTS, so that the covering has a sufficient edge for attaching to the skin and also sufficient interspaces in several areas and provides it with a removable protective layer. The materials used in this matrix system can be the same as in those of variant a.

A transdermal therapeutic reservoir system according to variant c can, for example, also be round, oval or rectangular and can be produced as follows;

An impermeable film is deformed by heat and/or traction, so that one to three bulges holding 0.1 to 3 ml result. The latter is filled with an active ingredient-containing solution or suspension containing 1-50% by weight of active ingredient or active ingredient mixture with a penetration-enhancing agent. The active ingredient-containing solution or suspension can also be thickened with up to 10% by weight of matrix former.

As a covering of the reservoir on the skin, a welded-on or bonded permeable polymer layer is used, to which a permeable skin contact adhesive layer and a removable protective layer are applied.

In this system, the above-mentioned penetration-enhancing agents can be used. As permeable polymer layer, for example, a 20 to 200 μm-thick film made of cellulose esters, cellulose ethers, silicones or polyolefin compounds is used. By variation of this polymer layer, the rate of diffusion of the active ingredient or active ingredient mixture can be varied within wide limits.

As adhesive and protective layer, the same materials are suitable, which are described in the transdermal therapeutic system according to variant a.

In the production of transdermal therapeutic systems with two or three active ingredient-containing matrix layers or pharmaceutical agent reservoirs arranged side by side, it is often suitable to introduce the 3-keto-desogestrel in one and estrogen or estrogens in the other. In such cases, the active ingredient-containing matrix systems or pharmaceutical agent reservoirs can contain not only different active ingredients, but in addition different penetration-enhancing agents.

In the case of the matrix systems according to variant a or b, care must be taken for a sufficient spacing of the areas to prevent a diffusion of the active ingredients in the respective other area. In the case of the reservoir systems according to variant c, it is possible to provide the individual reservoirs with different permeable polymer layers to match the diffusion flow of the individual active ingredients to the respective needs.

Other features of the transdermal systems according to the invention can be explained based on the attached drawings that are not true-to-scale.

Fig. 1 shows a cross section through a simple round matrix system according to variant a without the removable protective layer. It consists of impermeable cover coating 1 and pharmaceutical agent-containing matrix layer 2.

Fig. 2 shows a cross section through a matrix system according to variant b without the removable protective layer.

Fig. 3 shows a longitudinal section through this system. The system consists of covering 3, which is provided with a contact adhesive layer 4. Two pharmaceutical agent-containing matrix layers 6 and 8 are attached to this contact adhesive layer by impermeable coverings 5 and 7.

Fig. 4 shows a cross section through a round, single-chamber reservoir system according to variant c without the removable protective layer. It consists of impermeable cover coating 9, pharmaceutical agent reservoir 10, permeable polymer layer 11 and skin contact adhesive layer 12.

Fig. 5 shows a cross section through a round, two-chamber reservoir system according to variant c without the removable protective layer. It consists of impermeable cover coating 13, two half-round pharmaceutical agent reservoirs 14 and 15, permeable polymer layer 16 and skin contact adhesive layer 16.

Besides transdermal therapeutic systems, also other galenical preparations are suitable for transdermal administration of 3-keto-desogestrel.

An emulsion gel for transdermal administration consists, for example, of the active ingredient or active ingredient mixture, penetration-enhancing agents, emulsifiers (in which ambiphilic representatives of the penetration-enhancing agents can be used as emulsifiers) and optionally matrix formers. A typical compound consists of 0.1-25% by weight of active ingredient or active ingredient mixture, 0-10% by weight of emulsifier, 0-5% by weight of matrix former, 0 to 50% by weight of penetration-enhancing agents and water to 100% by weight. The agent is emulsified in the usual way, and mixed, if necessary, with the usual antioxidants, preservatives, etc.

Single-phase gels are obtained, for example, by dissolving or suspending the active ingredient or the active ingredient mixture in solvents, such as water, lower alcohols or their mixtures, optionally by adding penetration-enhancing agents and thickening with matrix formers.

Typical compounds for such gels contain 0.01-25% by weight of active ingredient or active ingredient mixture, 1-20% by weight of matrix formers, 0 to 40% by weight of penetration-enhancing agents supplemented with the solvent to 100% by weight.

Also, these gels can optionally contain antioxidants, preservatives, etc.

A typical spray compound is, for example, the following:

1-25% by weight of active ingredient or active ingredient mixture, 0-20% by weight of matrix former, 0-60% by weight of penetration-enhancing agents supplemented with solvents and

optionally foaming agents to 100%. If pressurized-gas packings are used, the foaming agent can be omitted.

The 3-keto-desogestrel-containing agents for transdermal administration according to the invention can be used for treating the same diseases as the previously known agents, for example, to be administered orally, which contain highly effective gestagens. Moreover, the optionally estrogen-containing preparations according to the invention also can be used for contraception. The agents according to the invention have special advantages in the treatment of diseases that require a long-term treatment with relatively high dosage of the active ingredients. Here, the frequency of administration can be significantly reduced and an essentially uniform blood plasma level can be achieved. Further, it is advantageous that no gastrointestinal side effects are to be expected, and in estrogen-containing combination preparations, the first liver passage is avoided, and that the dose of estrogen can be reduced.

These advantages make the estrogen-free monotherapeutic agents of this invention appear to be especially suitable to treat, for example, endometriosis, gestagen-dependent tumors, benign breast diseases or the premenstrual syndrome.

The transdermal use of estrogens in sequential or continuous combination with 3-keto-desogestrel offers special advantages, for example, for treating menopausal symptoms, for preventing osteoporosis, for regulation of the menstrual cycle and stabilization of the menstrual cycle.

The following embodiments are used for a more detailed explanation of the invention. The following commercial products are used in the embodiments:

Polyester film of 0.074 mm thickness (Skotchpak [Scotchpak](R) 1009) of manufacturer 3M; polypropylene film (Celgard(R) 2500) of manufacturer Celanese, Linerfolie Skotchpak [liner film scotchpak](R) 1022 and 1360 of manufacturer 3M; transfer adhesive 9871 of manufacturer 3M, polyacrylester adhesive of type Sichello(R) J 6610-21 of manufacturer Henkel KG, silicone adhesive of type X-7-2960 of manufacturer Dow Corning and hydroxypropyl cellulose of type Klucel(R) HXF of manufacturer Hercules, polyisobutylene of type Oppanol(R) B 15 SF of the BASF AG company.

Example 1

0.8 g of 3-keto-desogestrel

8.0 g of 1,2-propanediol

are introduced in succession with stirring in 62.4 g of a 50% solution of silicone adhesive in benzine. After degassing the batch, the mixture is applied by a coating device to polyester film, so that after removal of the volatile solvent, a uniform film of 40 g/m^2 of solid coating results. Then, it is laminated with a fluoropolymer-coated polyester liner. The thus obtained laminate is divided by a punching device into round individual plasters of 10 cm^2 area and packaged in aluminum foil. Fig. 1 shows a cross section through this plaster without polyester liner. After removal of the liner film, the plaster adheres to the skin.

The determination of content yields a uniform active ingredient distribution of 0.08 mg/cm^2 in the average.

Example 2

5.0 g of 3-keto-desogestrel and

10.0 g of isopropyl myristate

are dissolved in succession with stirring in 170 g of a 50% solution of polyacrylester adhesive in acetone/benzine. After degassing the batch, the solution is applied by a coating device to polyester film, so that after removal of the volatile solvent, a uniform film of 100 g/m^2 of solid coating results. Then, it is laminated with a siliconized active ingredient-free liner film. The thus obtained laminate is divided by a punching device into

individual plasters of 10 cm^2 area and packaged in aluminum foil. After removal of the liner film, the plaster adheres to the skin.

The content of desogestrel is 0.5 mg/cm^2 in the average.

Example 3

3.5 g of estradiol

3.5 g of 3-keto-desogestrel and

7.0 g of 1,2-propanediol with 10% 1-dodecanol

are dissolved or suspended in succession with stirring in 112 g of a 50% solution of polyacrylester adhesive in acetone/benzine. After degassing the batch, the mixture is applied by a coating device to polyester film, so that after removal of the volatile solvent, a uniform film of 70 g/m^2 of solid coating results. Then, it is laminated with a siliconized active ingredient-free liner film. The thus obtained laminate is divided by a punching device into individual plasters of 10 cm^2 area and packaged in aluminum foil. After removal of the liner film, the plaster adheres to the skin.

In a like manner, the content of estradiol and 3-keto-desogestrel is about 0.35 mg/cm^2 each.

Example 4

Analogously to example 1, two different segment-type matrix systems are produced, which have the design represented in fig. 2 and 3. Matrix system I consists of matrix layer 8 -- provided with a polyester film 7 -- of the following composition:

1.0 mg of 3-keto-desogestrel

5.0 mg of isopropyl myristate

44 mg of acrylate adhesive solid

and has an area of 5 cm^2.

Matrix system II consists of matrix layer 6 -- provided with a polyester film 5 -- of the following composition:

2.0 mg of 17ß-estradiol

10.0 mg of isopropyl myristate and

88 mg of acrylate adhesive solids

and has an area of 10 cm^2.

Both matrix systems are bonded to a linen cloth coated with a skin contact adhesive, as fig. 3 shows. After lamination and punching out, plasters of the type shown in fig. 2 and 3 result.

Example 5

A polyester film of a 7.4 cm diameter is deformed by traction and heat, so that a round bulge of 10 cm^2 area results. The latter is filled with 1 ml of a suspension of

2.5 mg of estradiol and

2.5 mg of 3-keto-desogestrel

in 1,2-propanediol, which contains 10% lauric acid. A polypropylene or cellulose acetate butyrate film is welded onto the edge. Depending on the pressure per time unit, the sealing temperature is between 70°C and 100°C. Contact adhesive film is transferred to the permeable polymer layer. The plaster is provided with a liner and packaged in aluminum foil.

Fig. 4 shows a cross section through a plaster of this type without liner.

From this plaster, in-vitro-release rates in water of 32°C of between 0.02 to 0.08 $\mu g/cm^2$/hour are achieved for both active ingredients equally.

Example 6

Analogously to example 5, a polyester film is deformed so that two half-round bulges of 7.5 cm^2 of area each, separated from one another by a web, result.

Reservoir I is filled with 0.75 ml of a suspension of

1.5 mg of 3-keto-desogestrel

in 1,2-propanediol

and reservoir II with 0.75 ml of such a suspension of

3.0 mg of 17β-estradiol

in 1,2-propanediol.

The further completion of the plaster takes place as described in example 5.

Fig. 5 shows a cross section through such a plaster without liner.

Example 7

0.2 g of 17β-estradiol

0.02 g of 3-keto-desogestrel

10.0 g of 1,2-propanediol and

10.0 g of isopropyl myristate

are dissolved in succession in 76.78 g of ethanol (96% by volume) or isopropanol. Then, 3 g of hydroxypropyl cellulose is added to the solution and the air is removed from it. After 2 hours of expanding time, the gel is bottled in aluminum tubes with three-fold inner protective varnishings.

The determination of content yields a homogenous active ingredient distribution in the gel with values of 95% at 105% of the setpoint value.

Example 8

20.00 g of 3-keto-desogestrel is dissolved in 1000 g of isopropyl myristate, sterilized by filtration and bottled in 5 ml medicine bottles under aseptic conditions.

Example 9

3.5 g of ethinylestradiol,

3.5 g of 3-keto-desogestrel and

7.0 g of isopropyl myristate

are incorporated in succession with stirring in 112 g of a 50% solution of polyisobutylene-plastic (Oppanol(R) B 15 SF of the BASF AG company) in acetone-benzine and worked-up as described in example 3.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Agent for transdermal administration, characterized in that it contains 3-keto-desogestrel, optionally in combination with one or more estrogen(s), together with a transdermal therapeutic system comprising two or three matrix layers adhering to a cover coating.

2. Agent for transdermal administration according to claim 1, wherein as estrogen(s), estradiol, estriol, 17α-ethinylestradiol, mestranol, 14α, 17α-ethanoestra-1,3,5(10)-triene-3β, 17α-diol, 14α, 17α-ethanoestra-1,3,5(10)-triene-3β, 16α, 17α-triol or esters of these compounds are used.

3. Agent for transdermal administration according to claim 2, wherein the transdermal therapeutic system consists of

a) an impermeable cover coating,
two or three matrix layer(s) adhering to the cover coating, containing the 3-keto-desogestrel, optionally estrogen(s) and optionally penetration-enhancing agents, permeable and self-adhesive for these components or covered or surrounded by a skin contact adhesive optionally containing penetration-enhancing agents, a removable protective layer, or

b) a covering provided with a contact adhesive optionally containing penetration-enhancing agents,
two or three matrix layer(s) (each) leaving uncovered a contact adhesive edge, attached by an impermeable covering to the contact adhesive, containing the 3-keto-desogestrel, optionally estrogen(s) and penetration-enhancing agents, and a removable protective layer, or

c) an impermeable cover coating,
two or three pharmaceutical agent reservoir(s) present on or in the cover coating and containing the 3-keto-desogestrel, optionally estrogen(s) and optionally penetration-enhancing agents.

two or three skin contact adhesive layers containing polymer layer(s), permeable to these components, of an optionally permeable penetration-enhancing agent, and a removable protective layer.

4. A process for the production of an agent for the transdermal administration of an active ingredient or active ingredient mixture according to claim 1 comprising combining 3-keto-desogestrel optionally in combination with one or more estrogen(s) in a transdermal therapeutic system, wherein said system contains two or three matrix layers.

5. A process for the production of an agent according to claim 4, wherein as estrogen(s), estradiol, estriol, 17α-ethinylestradiol, mestranol, 14α, 17α-ethanoestra-1,3,5(10)-triene-3β, 17α-diol, 14α, 17α-ethanoestra-1,3,5(10)-triene-3β, 16α, 17α-triol or esters of these compounds are used.

6. A process for transdermal contraception, for treating endometriosis, for treating gestagen-dependent tumors or for treating the premenstrual syndrome, comprising employing a transdermal therapeutic system according to claim 1.

7. A process for treating menopausal symptoms, for prevention of osteoporosis, for regulation of the menstrual cycle, for stabilization of the menstrual cycle or for transdermal contraception, comprising employing a transdermal therapeutic system according to claim 1.

DATED this 20th day of November, 1997.

SCHERING AG

By Its Patent Attorneys

DAVIES COLLISON CAVE

Abstract

An agent for transdermal administration is described, which is characterized in that it contains 3-keto-desogestrel optionally in combination with one or two estrogen(s).

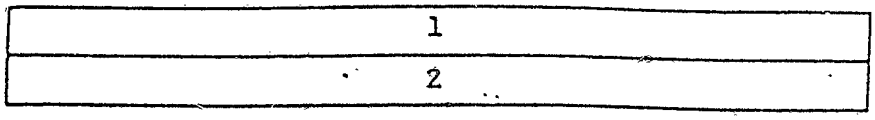


Fig. 1

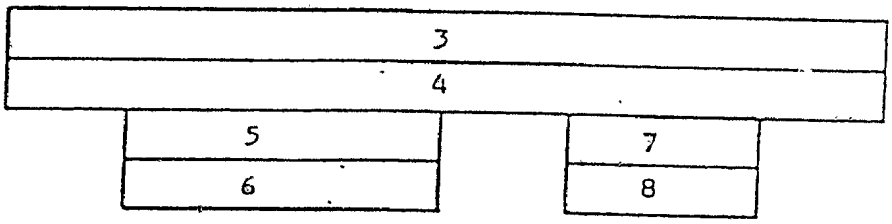


Fig. 2

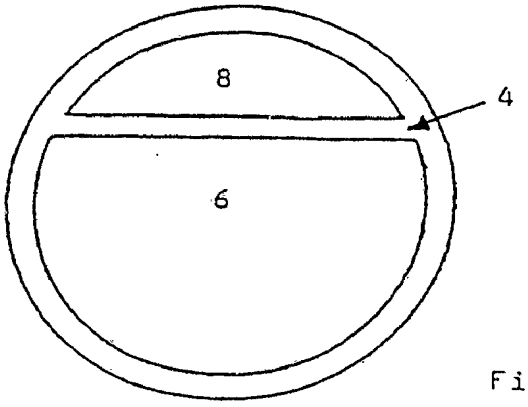


Fig. 3

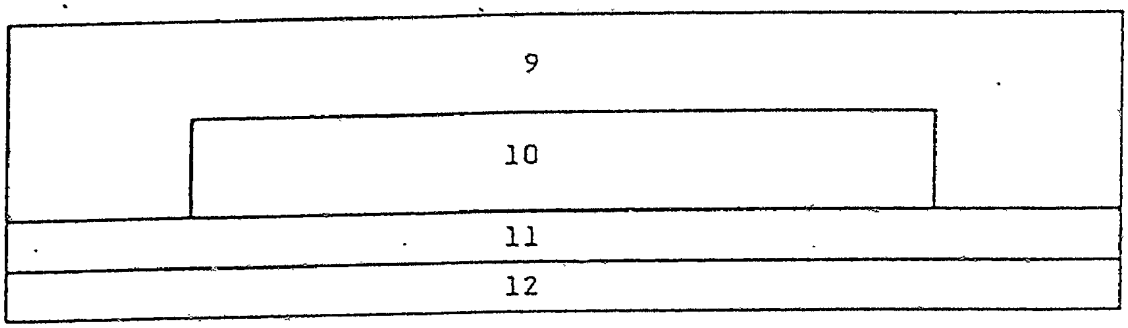


Fig. 4

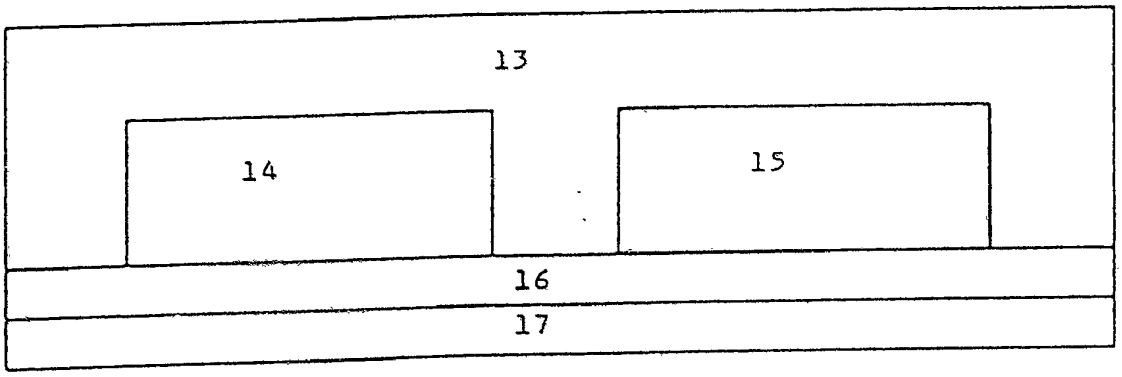


Fig. 5

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 93/02224

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/565 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 137 278 (SCHERING AG) 17 April 1985 see the whole document ---	1-13
Y	EP,A,0 253 607 (AMERICAN HOME PRODUCTS CORPORATION) 20 January 1988 see the whole document ---	1-11,13
Y	EP,A,0 491 443 (AKZO N.V.) 24 June 1992 see the whole document ---	1-13
Y	CONTRACEPTION vol. 42, no. 1 , 1990 pages 1 - 11 S.-E. OLSSON ET AL. 'Clinical results with subcutaneous implants containing 3-keto desogestrel' see the whole document --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1993	28. 12. 93.

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Krautbauer, B

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 491 438 (AKZO N.V.) 24 June 1992 see the whole document	1-11,13
Y	M. ROSOFF 'Controlled release of Drugs: Polymers and Aggregate Systems' 1989 , VCH PUBLISHERS , USA see page 277 - page 305	1-13
Y	LANCET vol. 335, no. 8685 , 1990 pages 310 - 312 M.I. WHITEHEAD ET AL. 'Transdermal administration of oestrogen/progestagen hormone replacement therapy' see abstract	1-13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
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